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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/090,965	03/04/2002	Friedrich Srien	110.01480101	6415

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EXAMINER
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PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

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10/19/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/090,965		SRIENC ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Yong D. Pak		1652	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 July 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Claims 1-13 are pending and are under consideration.

#### ***Response to Arguments***

Applicant's arguments filed July 20, 2007 have been fully considered but they are not persuasive.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Madison et al., Johnston et al., Clemente et al., and Linde et al.

Claims 1-13 are drawn to a method of producing PHA in *S. cerevisiae* or *Kluyveromyces* by introducing polynucleotide encoding a PHA<sub>SCL</sub> or PHA<sub>MCL</sub> and a polynucleotide encoding an acetoacetyl-CoA reductase and/or a  $\beta$ -ketothiolase.

Madison et al. teach a method of producing PHA in *S. cerevisiae* by introducing DNA encoding an *A. eutrophus* PHA polymerase (page 44). Madison et al. teach that low levels of PHA was due to insufficient activity of the endogenous  $\beta$ -ketothiolase and acetoacetyl-CoA reductase and points to improving PHA yields in *S. cerevisiae* by increasing the activities of these two enzymes.

Further, Madison et al. teach other PHA<sub>SCL</sub> and PHA<sub>MCL</sub> that can be used in transgenic yeasts (pages 24-35) and that many different transgenic organisms can be used to produce PHA (page 44), such as a *Kluyveromyces*, which also belongs to the family of Saccharomycetaceae like *S. cerevisiae*.

The difference between the reference of Madison et al. and the instant invention is that the reference of Madison et al. does not teach a method of producing PHA anaerobically using a yeast transformed a single nucleic construct comprising at least two of  $\beta$ -ketothiolase, acetoacetyl CoA reductase or PHA<sub>SCL</sub> or PHA<sub>MCL</sub>.

However, expression of multiple heterologous genes in yeast is routine in the art. Also, making a single nucleic acid construct composed of more than one or two genes

is also very routine in the art (Stratogene catalog, cited in previous Office Action). For example, Clemente et al. (U.S. Patent No. 5,489,894 – form PTO-892) discloses a method of expressing three genes via a single nucleic acid construct (Columns 15-16). Johnston et al. discloses using divergent promoters to express more than one gene in *S. cerevisiae*.

Regarding the limitation of producing PHA under anaerobic conditions, it is well known in the art that *S. cerevisiae* is able to grow both aerobically and anaerobically (Visser et al., Ohmori et al., Linde et al., Nissen et al.). It is also well known in the art that oxygen can cause serious stress to living organisms, including yeasts (Linde et al. and Nissen et al.). Linde et al. also discloses that gene expression in *S. cerevisiae* under anaerobic and anaerobic culture conditions showed little difference and that the yeast is unique among eukaryotes in exhibiting fast growth in both the presence and complete absence of oxygen (page 7412 and abstract). From the teachings in the art and Linde et al., one having ordinary skill in the art would have recognized to use transgenic *S. cerevisiae* and *Kluyveromyces*, under anaerobic or aerobic conditions, permitting flexibility in culture conditions.

Therefore, with the references of Madison et al., Johnston et al., Clemente et al., and Linde et al. in hand, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a transgenic *S. cerevisiae* or *Kluyveromyces* yeast comprising the heterologous PHA polymerase,  $\beta$ -ketothiolase and/or acetoacetyl CoA- reductase. The motivation of further expressing said enzymes via a single nucleic acid construct is to control and increase activity of said enzymes to

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increase the yield of PHA. The motivation of producing polyhydroxyalkanoates under anaerobic conditions would be to permit flexibility in culture conditions. One of ordinary skill in the art would have had a reasonable expectation of success since Madison et al. teach that an increase in activity of  $\beta$ -ketothiolase and an acetoacetyl CoA- reductase in yeast transformed with PHA<sub>SCL</sub> or PHA<sub>MCL</sub> will increase the yield of PHA, Clemente et al. and Johnston et al. both teach expression of multiple genes, and Linde et al. teaches flexibility of expressing genes in anaerobic and aerobic culture conditions.

Therefore, the above references render claims 1–13 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants agree that the claims are not obvious because it is unpredictable as to whether or not the metabolites would be produced upon changing the culturing conditions to an anaerobic one. Examiner respectfully disagrees. A skilled artisan would expect successful anaerobic production of PHAs. Lee et al. (Waste Management 19 (1999) 133-139 – cited previously on form PTO-892) discloses that a microorganism efficiently accumulates PHAs under oxygen limitation (page 134).

Applicants argue that the teachings of Linde et al. is irrelevant to the production of PHA. While Linde et al. does not mention PHA synthesis, Linde et al. provides the teaching that *S. cerevisiae* is unique among eukaryotes in exhibiting fast growth in both the presence and complete absence of oxygen (abstract). From this teaching, one

having ordinary skill in the art would have recognized to use transgenic *S. cerevisiae* and *Kluyveromyces*, under anaerobic or aerobic conditions, permitting flexibility in culture conditions and thereby improving cost effectiveness of producing PHA.

Applicants also argue that an artisan family with what is taught in this field would expect that anaerobic production of PHA would probably not be successful and that literature explicitly states that PHA engineering is unpredictable. However, applicants have not provided such evidence. In the absence of such evidence that production of PHA in *S. cerevisiae* under anaerobic conditions was difficult to achieve or that PHA are not produced in *S. cerevisiae* under anaerobic conditions, production of PHA in *S. cerevisiae* under anaerobic conditions would not be unexpected to one having ordinary skill in the art. Further, contrary to applicants argument, a skilled artisan would expect successful anaerobic production of PHAs. Lee et al. (Waste Management 19 (1999) 133-139 – form PTO-892) discloses that a microorganism efficiently accumulates PHAs under oxygen limitation (page 134).

Further, MPEP 2143.02 states that "Obviousness does not require absolute predictability". Since *S. cerevisiae* are able to grow during anaerobic conditions, Linde et al. teach that there is little difference of aerobic and anaerobic transcript profiles of *S. cerevisiae* and the ability for *S. cerevisiae* to produce PHA under anaerobic condition is inherent to the yeast, in the absence of any evidence that production of PHA in *S. cerevisiae* under anaerobic conditions was difficult to achieve or that PHA are not produced in *S. cerevisiae* under anaerobic conditions, production of PHA in *S. cerevisiae* under anaerobic conditions would not be unexpected to one having ordinary

skill in the art. Rather, with the teachings of Linde et al., one having ordinary skill in the art would have been motivated to culture yeasts under anaerobic or aerobic conditions determine if genes involved in PHA synthesis have different transcript profiles under aerobic or anaerobic conditions, thereby altering yield of PHA.

Applicants also argue that the cited references the examiner is applying an improper "obvious to try" rationale in support of an obviousness rejection. Examiner respectfully disagrees. In the instant case, the claimed method is obvious over the prior arts relied upon because said references contains proper suggestion to modify the prior art to produce the claimed invention. See MPEP 2145.

Hence the rejection is maintained.

### ***Conclusion***

Claims 1-3 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.



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Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).



Yong D. Pak  
Patent Examiner 1652